General

Guideline Title

ACR Appropriateness Criteria® nasopharyngeal carcinoma.

Bibliographic Source(s)

Saba NF, Salama JK, Beitler JJ, Busse PM, Cooper JS, Jones CU, Koyfman S, Quon H, Ridge JA, Siddiqui F, Worden F, Yao M, Yom SS, Expert Panel on Radiation Oncologyâ€“Head & Neck Cancer. ACR Appropriateness CriteriaÂ® nasopharyngeal carcinoma. Reston (VA): American College of Radiology (ACR); 2015. 13 p. [69 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Nasopharyngeal Carcinoma

Variant 1: A 70-year-old man presents with a T3N2M0 EBV-positive nonkeratinizing NPC. He completes a definitive course of IMRT to a prescribed dose of 6996 cGy in combination with concurrent cisplatin (100 mg/m^2 for 3 doses) but requires 2 dose reductions and experiences one brief hospitalization near the end of treatment due to severe mucositis, dehydration, and need for feeding tube placement.

Treatment	Rating	Comments
No further therapy	6	
Testing of EBV DNA level and recommendation for adjuvant therapy if test is positive	5	NRG HN001 is testing this, but until the result of this trial is available, standard treatment is still 3 cycles of adjuvant chemotherapy. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		
Adjuvant cisplatin, 5-FU	1	Usually not appropriate as patients could not complete adjuvant chemotherapy. This procedure may be appropriate but there was disagreement among panel members on the

Treatment	Rating	Comments
		appropriateness rating as defined by the panel's median rating.
Break for 3 months, then adjuvant cisplatin/5-FU × 3 cycles	3	
SRT to boost the skull base	3	Toxicities were considerable.
Adjuvant therapy with paclitaxel and carboplatin	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: A 35-year-old woman presents with worsening otitis and a bulky right-sided neck mass extending into the supraclavicular fossa. Endoscopy of the nasopharynx reveals a 3-cm infiltrative-appearing tumor centered in the right fossa of Rosenmüller, and biopsy shows undifferentiated carcinoma of the nasopharynx that is EBV positive. MRI shows that the primary tumor is invading into the parapharyngeal space and there are bilateral 1-cm retropharyngeal nodes, 2-cm adenopathy on the left, and 5-cm adenopathy on the right (T2N3bM0, stage IVB). There is no evidence of distant disease on CT of the chest and bone scan. Karnofsky Performance Status (KPS) is 90%.

Treatment	Rating	Comments
Cisplatin/5-FU followed by concurrent cisplatin-based chemoradiation	5	This procedure requires confirmation through a phase III trial.
Docetaxel/platinum/5-FU followed by concurrent cisplatin-based chemoradiation	4	This procedure requires confirmation through a phase III trial.
Concurrent cisplatin-based chemoradiation	5	Three published studies favor the concurrent approach but do not negate the induction or adjuvant approaches. This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Concurrent cisplatin-based chemoradiation followed by adjuvant chemotherapy	8	
Definitive RT alone	1	Three published studies negate the validity of radiation alone.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 3: A 38-year-old man presents with nasal congestion and left-sided otitis. Endoscopy shows a tumor centered in the left fossa of Rosenmüller, and the biopsy is read as undifferentiated NPC, EBV positive. An MRI shows erosion of the sphenoid sinus but no intracranial involvement, with 2-cm left retropharyngeal adenopathy and bilateral enlarged jugulodigastric nodes. The chest CT shows no pulmonary parenchymal metastasis, but a bone scan shows an isolated 2-cm lesion that is biopsy-proven metastatic disease in the lumbar spine with no compression (T3N2M1). He does not complain of back pain and his neurologic examination is normal. He is not interested in a clinical trial.

Treatment	Rating	Comments
Definitive chemoradiation therapy to the nasopharynx and neck, followed by adjuvant chemotherapy	4	The first logical step, however, is a biopsy to prove the metastatic nature of the spine lesion. The ratings, therefore, reflect the presumed positivity.
Chemotherapy followed by definitive RT to the nasopharynx and neck and palliative RT to the spine	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Emergent palliative RT to the spine followed by chemotherapy	3	
Chemotherapy only	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Chemotherapy followed by palliative-dose RT to the nasopharynx, neck, and spine	5	
Definitive chemoradiation therapy to the nasopharynx and neck, followed by chemotherapy as well as definitive radiation to the spinal lesion	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Definitive chemoradiation therapy to the nasopharynx and neck as well as definitive radiation to the spinal lesion	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 4: A 22-year-old man is admitted to the hospital because of a 30-pound weight loss in a period of 3 months, with mild constant headaches. CT scan of the head reveals a nasopharyngeal lesion. MRI of the brain and orbits shows an infiltrating mass with extra-axial intracranial and extracranial extension. There is involvement along the dura, multiple cranial nerves, orbits, adjacent osseous structures, nasopharynx, and nasal cavity, with bilateral cervical lymphadenopathy. His tumor biopsy reveals an EBV-positive undifferentiated NPC. He undergoes 3 cycles of cisplatin with concurrent RT and has an excellent response, with resolution of symptoms. On a follow-up scan 6 months after completion of therapy, he does not have evidence of local progression, but there are 2 lung metastases as well as mediastinal nodal disease. He is asymptomatic and has an excellent PS.

Treatment	Rating	Comments
Platinum doublet	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Cisplatin, 5-FU and cetuximab (the EXTREME regimen)	3	Nasopharyngeal patients were excluded from the EXTREME study.
Single-agent gemcitabine	4	The first choice is a platinum doublet, not a single agent.
Single-agent paclitaxel	4	The first choice is a platinum doublet, not a single agent.
Single-agent multitargeted TKI	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 5: A 45-year-old man is diagnosed with T3N1M0 keratizing carcinoma of the nasopharynx. He is treated with definitive chemoradiation to a maximum prescribed dose of 70 Gy to the nasopharynx, given in conventional fractionation with 3D-CRT, with concurrent cisplatin at 100 mg/m^2 for 3 cycles, followed by 3 cycles of adjuvant cisplatin/5-FU. At 14 months after finishing his RT, the patient complains of worsening numbness in his face. MRI reveals an infiltrative tumor causing mild erosion of the clivus and an enlarging area of bone erosion at the right foramen ovale, with enhancement suggestive of perineural recurrence.

Treatment	Rating	Comments
IMRT	6	
IMRT with concurrent chemotherapy	7	
Induction chemotherapy followed by IMRT	3	
SRT	6	
Intracavitary brachytherapy	1	
Nasopharyngectomy	2	
Chemotherapy only	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.

Treatment	Rating	Comments
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

Variant 6: A 22-year-old woman presents with severe headaches and left-sided diplopia. MRI reveals a large skull base tumor originating from the nasopharynx, with abutment against the posterior aspect of the bilateral optic nerves and partial engulfment of the optic chiasm. There is bilateral cavernous sinus involvement, worse on the left. There are bilateral 1–2 cm jugulodigastric lymph nodes that are FDG-avid on PET/CT scan (T4N2M0, stage IVB). Nasopharyngeal biopsy reveals keratinizing carcinoma. KPS is 80%. She is started on dexamethasone, with partial improvement of her symptoms.

Treatment	Rating	Comments
Concurrent chemoradiation followed by adjuvant chemotherapy	7	
Induction chemotherapy followed by concurrent chemoradiation	6	This procedure requires confirmation through a phase III trial.
Definitive conventionally fractionated RT with SRT boost	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

See the tables in the original guideline document for references supporting the comments.

Summary of Literature Review

Epidemiology and Risk Factors of Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a rare disease in the Western world, with an incidence in the United States of 0.5–2 per 100,000. However, the incidence of NPC is significantly higher in southern China, southeast Asia, and the Middle East/North Africa, where it is one of the most common cancers. This geographic variation suggests interactions of different factors such as Epstein-Barr virus (EBV) infection, genetic predisposition, and environmental factors including diet, which are more likely to be found in combination in endemic regions. In the Western world, some of the incidence may be driven by classic risk factors common to most head and neck cancers, such as tobacco use or alcohol consumption, but the highest incidence rates are still found in Asian immigrant populations. The incidence of NPC peaks around ages 50 to 59 and then declines. However, an increased incidence of NPC in younger individuals in endemic regions suggests that affected individuals may carry a genetic predisposition towards EBV infection early in life, leading to an increased predisposition to NPC. NPC cells express EBV latent proteins, such as EBNA-1, LMP-1, and LMP-2, as well as BamHI, a fragment of the EBV genome. It is thought that viral proteins may induce epithelial cellular growth following exposure to EBV, with secondary genetic alterations occurring with exposure to environmental carcinogens later in life.

Clinical Presentation and Evaluation

NPC patients commonly present with headache, cranial nerve involvement, nasal obstruction, or a neck mass due to nodal metastases. However, patients may remain asymptomatic for a long time, given the often clinically occult site of presentation. When a patient is suspected of having NPC, endoscopic visualization of the primary tumor should be the initial step. Most tumors arise in the lateral nasopharyngeal wall in the fossa of Rosenmüller. Endoscopic biopsy should be performed. In the most recently modified World Health Organization (WHO) classification, the category of squamous cell carcinoma subtype (keratinizing squamous cell carcinoma) was retained, while the other 2 subtypes were combined under a single category of "nonkeratinizing carcinoma," which was further subdivided as being "differentiated" or "undifferentiated." In addition, lymphoepithelioma-like carcinoma was considered a morphologic variant of undifferentiated carcinoma. The use of numerical designations of WHO types 1, 2, and 3 was also eliminated in the most recent classification, and the subtype of basaloid squamous cell carcinoma was added. NPC is clinically staged according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). To assess the locoregional extent of disease, imaging for NPC patients usually should include magnetic resonance imaging (MRI) of the nasopharynx, skull base, and neck. The upper mediastinum should also be imaged if there are low neck nodal metastases. Although computed tomography (CT) can detect mass lesions in the nasopharynx, MRI is superior at detecting the extent of osseous cranial nerve and intracranial involvement, which is critical given the propensity for skull base invasion and intracranial spread. As NPC tends to metastasize early, with distant metastases having a reported frequency of up to 11%, additional imaging with positron emission tomography (PET) may be helpful. In a case where a PET scan is not available, a bone scan and CT scan of the chest and abdomen is recommended. In light of the evidence supporting measurement of baseline and post-treatment plasma EBV deoxyribonucleic acid (DNA) levels to monitor response and recurrence, a pretreatment and post-treatment EBV

DNA level may be appropriate; the value in guiding therapy is the subject of an ongoing NRG protocol.

General Treatment for Nasopharyngeal Carcinoma

Given that most patients present with locoregionally advanced disease not amenable to definitive surgical resection as well as the inherent morbidity of surgical resection in the nasopharynx, most patients with NPC are treated with radiation with or without chemotherapy. Surgery is typically reserved for salvage of post-radiation therapy recurrences and can be combined with brachytherapy or other forms of reirradiation. Interestingly, in the United States, Asians have the highest rate of receiving radiation only, which was significant in the multivariate stratified analysis; it is unclear if this is due to an unfit or elderly age distribution in this population or a cultural or socioeconomic factor resulting in higher levels of guideline-discordant care.

Treatment of Stage I (Early) Disease

NPC is a radiosensitive tumor, and early-stage disease (T1N0) is usually treated with radiation therapy (RT) only. Traditionally, 3-D conformal radiation therapy (3D-CRT) has been used for treating early-stage NPC, but recent randomized studies point to the benefits of intensity-modulated radiation therapy (IMRT) in avoiding late toxicities such as xerostomia. In one randomized study comparing 3D-CRT with IMRT for early-stage NPC patients, the European Organisation for the Research and Treatment of Cancer (EORTC) core questionnaire and EORTC quality-of-life module for head and neck cancer (QLQ-H&N35) were completed at baseline and 2, 6, and 12 months after RT to assess for differences in toxicity based on radiation technique. At 12 months post-RT, more patients had recovered at least 25% of pre-RT stimulated whole saliva, 12 (50.0%) in the IMRT group compared to 1 (4.8%) in the 3D-CRT group. Furthermore, recovery of 25% of pre-RT stimulated parotid saliva flow was seen in 20 patients (83.3%) in the IMRT group and 2 patients (9.5%) in the 3D-CRT group. This study confirms that IMRT was superior to 3D-CRT in terms of parotid sparing and improved quality of life for early-stage disease. In a second study of 60 patients with stages T1–2bN0–1M0, patients were randomized to either IMRT or 2D-CRT. At 1 year after treatment, patients in the IMRT arm had a lower incidence of severe xerostomia based on the Radiation Therapy Oncology Group®/EORTC late radiation morbidity scoring criteria compared to patients receiving 2D-CRT therapy (39.3% versus 82.1%; P=0.001). Regarding intensity-modulated proton therapy in NPC, mature clinical data is lacking, although some institutions have started performing comparative studies between the 2 modalities; in the main, it remains a largely experimental approach.

Early-stage NPC is curable with RT alone, with a 5-year overall survival (OS) of close to 90% for stage I disease. Even though a noted improvement in outcome in recent years can be attributable to better staging modalities and stage migration, an improvement in radiation planning and delivery techniques likely explains at least some of this improvement. It is unclear if adjuvant or neoadjuvant systemic therapy would offer any benefit to patients with early-stage NPC, as very few patients with stage I or early stage II disease have been included in clinical trials examining this question.

Treatment of Stage II (Intermediate) Disease

Patients with stage II NPC (T1N1, T2N0-1), especially those with node-positive disease, have a substantial rate of distant metastases, and therefore concurrent chemotherapy and RT is recommended. In a study involving 230 stage II (Chinese staging of 1992) NPC patients (T1-2N1 or T2N0 with parapharyngeal space involvement), participants were randomized to RT alone (n =114) or RT with concurrent cisplatin (n =116) (CCRT). Patients on the CCRT arm received cisplatin (30 mg/m^2 weekly during CRT) and had a statistically significant improvement in the 5-year OS rate (94.5% versus 85.8%, P=0.007), progression-free survival (PFS) rate (87.9% versus 77.8%, P=0.017), and distant metastasis–free survival rate (94.8% versus 83.9%, P=0.007). There was, however, no difference noted in the 5-year locoregional relapse–free survival rate (93.0% versus 91.1%, P=0.29). The main contributor to the improvement in OS was the significant reduction in the rate of distant metastases. Furthermore, on multivariable analysis the only independent factor associated with OS, PFS, and distant control was the number of chemotherapy cycles administered. As one might expect, chemotherapy leading to improvements in outcome also resulted in increased acute toxicity. Fortunately, no clear increase in chronic toxicities was observed. These findings support concurrent chemoradiotherapy as the treatment of choice for patients with stage II NPC. As patients with T2N1 disease appear to have a higher distant metastasis risk compared to patients with T2N0 and T1N1 disease, the use of systemic therapy for patients with T2N1 disease is more justifiable.

Treatment of Stage III or IV (Advanced) Disease

Concurrent Chemoradiotherapy

Concurrent chemotherapy and radiation is the backbone of treatment of locally advanced NPC. One of the early trials comparing radiation alone to concurrent chemoradiotherapy was the phase III Intergroup 0099 study randomizing patients to RT only (1.8 to 2.0 Gy per day for 35 to 39 fractions, for a total dose of 70 Gy) versus RT plus chemotherapy. Of note, the RT was delivered using opposed lateral beams, not IMRT. The chemotherapy regimen consisted of cisplatin 100 mg/m^2 on days 1, 22, and 43 during RT, followed by cisplatin 80 mg/m^2 on day 1 and 5-

fluorouracil (5-FU) 1000 mg/m^2/day on days 1 to 4, administered every 4 weeks for 3 cycles after RT. Although only 63% of patients completed 3 cycles of concurrent therapy and only 55% completed adjuvant chemotherapy, by intention-to-treat analysis, the use of concurrent chemotherapy dramatically improved both PFS and OS. The median PFS time was 15 months for eligible patients on the RT arm and was not reached for the chemoradiotherapy group. Furthermore, the 3-year PFS rates were 24% and 69%, respectively (P<0.001). The median survival time was 34 months for the RT arm and was not reached for the chemoradiotherapy arm, and the 3-year survival rates were 47% versus 78%, respectively (P=0.005).

Other studies have confirmed the basic findings of the Intergroup 0099 study, demonstrating its applicability to endemic NPC regions and confirming the essential role of concurrent therapy. However, the difficulty of administering a concurrent and adjuvant chemotherapy regimen remains a challenge due to acute and late toxicities. This has led to an increased interest in investigating the efficacy of alternative cisplatin dosing schedules or alternative systemic agents combined with RT. A single-center noninferiority trial compared carboplatin 100 mg/m^2/day with cisplatin 100 mg/m^2/day in the concurrent setting. Following the completion of chemoradiation, those assigned to the carboplatin arm received carboplatin at area under the curve dose 5 intravenously and 5-FU infusion at 1000 mg/m^2/day by 96-hour infusion every 4 weeks for a total of 3 cycles, and those in the cisplatin arm received cisplatin 80 mg/m^2 intravenously and 5-FU infusion at 1000 mg/m^2/d by 96-hour infusion every 4 weeks for a total of 3 cycles, both beginning 4 weeks after the end of RT. The efficacy of the 2 regimens was equivalent, with carboplatin better tolerated, with less renal toxicity, nausea, vomiting, and anemia. Confirmation trials are needed, as the confidence intervals for survival in this trial were rather wide. Additionally, as RT with weekly cisplatin has been found to be superior to radiation alone in randomized trials conducted in endemic regions, many Asian centers have adopted weekly concurrent cisplatin as a standard clinical practice, although the weekly regimen has not been compared head to head against the standard of 100 mg/m^2 cisplatin every 3 weeks.

Sequencing of Additional Chemotherapy with Chemoradiotherapy

Although meta-analysis results in the wake of Intergroup 0099 confirm the positive effects of concurrent chemoradiotherapy, the role of chemotherapy in the neoadjuvant or adjuvant setting remains a topic of debate. Adjuvant systemic therapy following concurrent chemoradiotherapy was assessed in a study from China in which a total of 251 patients were assigned to concurrent chemoradiotherapy followed by adjuvant chemotherapy, and another 257 patients were assigned to chemoradiotherapy only. Approximately 20% of the patients in the adjuvant arm did not receive chemotherapy per protocol. After a median follow-up of 37.8 months, the 2-year failure-free survival rate was 86% in the concurrent-adjuvant group versus 84% in the concurrent group (P=0.13). Although the data suggest that adjuvant chemotherapy may not be beneficial, it must be noted that this study was not designed as a noninferiority study against the standard. Hence, it is difficult to draw definitive conclusions. Given the fact that plasma EBV DNA levels have prognostic value in patients with recurrent metastatic NPC, there is increasing interest in stratifying the care of patients based on the detectability of EBV after definitive concurrent therapy. NRG HN 001 randomizes patients with undetectable EBV after their definitive chemoradiotherapy to either chemotherapy with cisplatin and 5-FU versus observation. On the other hand, patients with detectable EBV will be randomized to cisplatin/5-FU versus gemcitabine/paclitaxel. The study will enroll patients in North America as well as Asia and may help answer the question of whether adjuvant chemotherapy can be omitted, at least for a selected group of patients with undetectable EBV. The study could better define the role of EBV titers in determining the most appropriate therapeutic choices after chemoradiotherapy; however, 1 issue remains: the need for harmonization of the polymerase chain reaction (PCR) assays for detection of EBV (see Variant 1 above).

As adjuvant chemotherapy on Intergroup 0099 was poorly tolerated and may not be the main factor in the improved survival seen in this study, chemotherapy given prior to chemoradiotherapy, also called neoadjuvant or induction therapy, has been proposed as a possible alternative.

Several phase II studies have attempted the induction approach with acceptable outcomes and toxicity profiles. A randomized phase II trial comparing induction chemotherapy followed by concurrent therapy to concurrent therapy only provided encouraging results, with a possible positive impact on survival. However, this requires confirmation in the phase III setting. In a trial investigating a radiation fractionation question, 50 patients with stage III and IV disease were treated with an induction chemotherapy approach, with response to induction being strongly predictive for locoregional control, disease-free interval, and OS. In a randomized phase II study completed in Hong Kong, induction docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were administered every 3 weeks for 2 cycles, followed by cisplatin at 40 mg/m^2/week given concurrently with RT; this was compared to concurrent therapy only. The 3-year PFS rates for the induction versus concurrent-only arms were 88.2% versus 59.5% (hazard ratio [HR] =0.49; 95% confidence interval [CI], 0.20–1.19; P=0.12), and the 3-year OS rates were 94.1% versus 67.7% (HR =0.24; 95% CI, 0.078–0.73; P=0.012), favoring the induction arm. GORTEC is completing a multicenter phase III trial comparing induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiotherapy to concurrent chemoradiotherapy alone for patients with T2b, T3, or T4 NPC with lymph node involvement (≥N1). The results of a recently completed randomized trial of induction therapy with gemcitabine, carboplatin, and paclitaxel failed to show an advantage to induction therapy. Another recently reported trial (NPC-0501) failed to show a benefit in changing the sequence of therapy from a concurrent-adjuvant to an induction-concurrent approach (see Variant 2 above).

Alternative Radiation Schedules

The current standard radiation schedule for NPC is 70 Gy in 2 Gy fractions given daily. Although meta-analyses have suggested improved outcomes with accelerated or hyperfractionated regimens for head and neck cancers in general, these have not been widely adopted in NPC. The role of accelerated fractionation in patients with NPC was investigated in a 4-arm randomized trial and appeared to offer an advantage in the concurrent-adjuvant chemotherapy arm with accelerated radiation, achieving a reduction in local failure and cancer-specific deaths. NPC-0501 investigated the role of accelerated fractionation in addition to systemic therapy and concluded that acceleration is not recommended in locoregionally advanced NPC. Despite these findings, other studies have revealed increased toxicity, especially to the central nervous system and skin, without a clear benefit in outcome when using accelerated approaches. Many studies have reported excellent locoregional control with the use of IMRT, with reduced xerostomia establishing this as a standard modality in NPC. Of note, most centers employ IMRT using a simultaneous integrated boost technique, which typically enacts a mild acceleration of the radiation dose to gross disease volumes. In addition, replanning during IMRT can improve the quality of life for patients with NPC.

Treatment of Recurrent and Metastatic Disease

As NPC is a chemosensitive disease with a response rate approaching 80%, systemic chemotherapy is considered the standard of care for patients who have metastatic disease as well as those with locoregionally recurrent disease who are not candidates for further locoregional therapy. In general, combination therapies that include a platinum agent have been noted to produce superior benefits compared to single-agent therapies. Despite the fact that the results of the EXTREME regimen revealed a survival advantage by adding cetuximab to a platinum-based regimen in squamous cell carcinoma of the head and neck, this is not a recommended approach in NPC, given that this trial did not include patients with this disease. However, no randomized trials have established a standard regimen for patients with recurrent metastatic NPC. In a large single-institution retrospective study, several regimens were compared, including cisplatin + 5-FU, paclitaxel + cisplatin, gemcitabine + cisplatin, paclitaxel + cisplatin + 5-FU, and bleomycin + cisplatin + 5-FU. No statistically significant differences were observed in PFS (P=0.247) or OS (P=0.127) among the different groups in this retrospective analysis. Recent evidence suggests that ERCC1 C8092A polymorphism can predict PFS in metastatic/recurrent NPC treated with cisplatin. The performance status of patients and their history of previous chemotherapy play a significant role in deciding which chemotherapy regimen would be most appropriate and whether single- or double-agent regimens would be more suitable. Of note is that plasma EBV DNA levels have been shown to have prognostic value in patients with recurrent or metastatic NPC and can be used as a prognostic tool when obtained serially at time points prior to therapy initiation as well as at follow-up visits (see Variant 3 and Variant 4 above). For patients with known metastatic disease to the bone, the use of bisphosphonates is advocated.

Second-line chemotherapy can be considered for patients with progression of disease following first-line therapy, as several agents have been shown to have activity in metastatic NPC. Potential choices include taxanes, gemcitabine, capecitabine, methotrexate, irinotecan, and vinorelbine.

Tyrosine kinase inhibitors (TKIs) have also been shown to have clinical activity in recurrent disease, but none of these agents have been approved for this indication. The overall response rate, if the outcome of stable disease is included, has been reported as high as 54%. The use of TKIs in NPC remains largely within the clinical trial setting. TKIs have also been used in combination with cytotoxic chemotherapy in the recurrent or metastatic setting, but this combination approach should similarly not be considered outside of a clinical trial. The high incidence of hemorrhage observed in some studies using antivascular agents has precluded the further development of these drugs for recurrent or metastatic NPC.

Local recurrence is a major cause of mortality and morbidity, despite advances in treating locally advanced disease. The best salvage treatment for locally recurrent NPC is unclear and should be determined on a case-by-case basis. Options for salvage include brachytherapy, external radiation therapy, stereotactic radiation therapy (SRT), and nasopharyngectomy. Reirradiation of the primary site or salvage surgery, if technically feasible, should be considered for treatment of local or regional recurrences, and these have been performed for selected patients with recurrent T1 or T2 disease (see Variant 5). A nasopharyngectomy via a maxillary swing approach has been investigated and can be considered if carefully tailored to individual cases.

Reirradiation should be performed in selected centers with expertise. Recent studies suggested that reirradiation with IMRT may offer long-term control, with a 2-year locoregional recurrence–free survival rate close to 65%. This was at the price of moderate to severe late toxicities in up to 35.7% of reirradiated patients. The decision to proceed with reirradiation has to be weighed very carefully against potential toxicity and ought to be done in centers with technical and supportive care expertise. Factors affecting the decision to reirradiate include performance status, prior RT dose, and the expected remaining tolerance of normal tissues. Even though IMRT has been used in this setting, there is no clearly adopted standard of radiation technique used to treat the recurrent disease. Fractionated SRT may provide excellent local control, although toxicities have always been a concern. The rate of long-term toxicity may be as low as 5.3% in selected patients treated at experienced centers. However, there is no clear consensus on what constitutes an optimal fractionation regimen. In a recent large retrospective report, the 5-year OS and distant metastasis–free survival rates were significantly higher when a program of endoscopic nasopharyngectomy and IMRT was compared to conventional 2-D RT. Brachytherapy for recurrent node-negative T1 or T2 disease has been effective in salvaging a selected group of patients. A high rate of local control with low morbidity is possible if rigorous selection processes are applied. No randomized trials have been performed in this clinical setting,

and there are few recommendations. Major late complication rates as high as 35% have been reported in some retreatment series, stressing the need to restrict these approaches to a very select patient population treated in centers with expertise (see Variant 6 above).

Summary of Recommendations

- Patients with locally advanced NPC who had poor tolerance to initial concurrent therapy can either omit adjuvant chemotherapy or receive it, provided it can be administered in a timely manner and they have a good recovery from their toxicity.
- Patients with locally advanced and bulky, invasive NPC are almost always treated with concurrent chemoradiation, although sequential or adjuvant approaches are also acceptable modalities.
- Patients with NPC presenting with an isolated bone focus of metastatic disease may achieve lengthy progression-free survival when treated with definitive concurrent chemoradiation to the primary site as well as definitive radiation (or stereotactic body radiation therapy [SBRT]) to the metastatic bone disease.
- A platinum doublet is the most accepted standard systemic regimen for recurrent or metastatic NPC.
- Nasopharyngectomy, SRT, IMRT alone, or IMRT with concurrent chemotherapy are all acceptable modalities in the management of locally recurrent NPC in the absence of distant disease.

Abbreviations

- CT, computed tomography
- 3D-CRT, 3-dimensional conformal radiation therapy
- DNA, deoxyribonucleic acid
- EBV, Epstein-Barr virus
- FDG, fludeoxyglucose
- 5-FU, 5-fluorouracil
- IMRT, intensity-modulated radiation therapy
- MRI, magnetic resonance imaging
- NPC, nasopharyngeal carcinoma
- PET, positron emission tomography
- RT, radiation therapy
- SRT, stereotactic radiation therapy
- TKI, tyrosine kinase inhibitors
- TNM, tumor, lymph node, metastasis

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Nasopharyngeal carcinoma (NPC)

Guideline Category

Treatment

Clinical Specialty

Internal Medicine

Oncology

Otolaryngology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Health Plans

Hospitals

Managed Care Organizations

Physician Assistants

Physicians

Students

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of treatment procedures for patients with nasopharyngeal carcinoma (NPC)

Target Population

Patients with nasopharyngeal carcinoma (NPC)

Interventions and Practices Considered

1. No further therapy
2. Testing of Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) level and recommendation for adjuvant therapy if test is positive
3. Adjuvant therapy
4. Chemotherapy
5. Radiation therapy (RT)
6. Concurrent chemoradiotherapy
7. Nasopharyngectomy

Note: See the Variant tables in the "Major Recommendations" field for specific intervention options.

Major Outcomes Considered

- 3-and 5-year overall survival rate
- Relapse-free survival rate
- Distant metastasis-free survival rate
- Median survival time
- Local and regional recurrence rate
- Toxicities

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Summary

A literature search was conducted in June 2011 and updated in May 2015 to identify evidence for the *ACR Appropriateness Criteria® Nasopharyngeal Carcinoma* topic. Using the search strategies described in the literature search companion (see the "Availability of Companion Documents" field), 216 articles were found. Six articles were used in the topic. Two hundred ten articles were not used due to either poor study design, the articles were not relevant or generalizable to the topic, or the results were unclear, misinterpreted, or biased.

The author added 63 citations from bibliographies, Web sites, or books that were not found in the literature search.

See also the American College of Radiology (ACR) Appropriateness Criteria® literature search process document (see the "Availability of Companion Documents" field) for further information.

Number of Source Documents

A literature search conducted in June 2011 and updated in May 2015 identified six articles that were used in the topic. The author added 63 citations from bibliographies, Web sites, or books that were not found in the literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Definitions of Study Quality Categories

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - The study has important study design limitations.

Category 4 - The study or source is not useful as primary evidence. The article may not be a clinical study, the study design is invalid, or conclusions are based on expert consensus.

> The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
>
> *Or*
>
> The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
>
> *Or*
>
> The study is an expert opinion or consensus document.

Category M - Meta-analysis studies are not rated for study quality using the study element method because the method is designed to evaluate individual studies only. An "M" for the study quality will indicate that the study quality has not been evaluated for the meta-analysis study.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND/UCLA Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. An initial survey is conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness (additional assumptions regarding rating appropriateness can be found in the document Rating Round Information). When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the first rating round, a conference call is scheduled to discuss the evidence and, if needed, clarify the variant or procedure description. If there is still disagreement after the second rating round, the recommendation is "may be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized, and economical process. For additional information on the ratings process see the Rating Round Information document.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria (AC).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current medical evidence literature and the application of the RAND/UCLA appropriateness method and expert panel consensus.

Summary of Evidence

Of the 69 references cited in the *ACR Appropriateness Criteria® Nasopharyngeal Carcinoma* document, 67 are categorized as therapeutic references including 25 well designed studies, and 22 good quality studies. Additionally, 2 references are categorized as diagnostic references including one good quality study. There are 21 references that may not be useful as primary evidence.

While there are references that report on studies with design limitations, 48 well designed or good quality studies provide good evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate treatment procedures for treatment of nasopharyngeal carcinoma (NPC)

Potential Harms

- Potential radiation therapy (RT) toxicities (e.g., xerostomia)
- Potential chemotherapy toxicities (e.g., renal toxicity, nausea, vomiting, and anemia)
- The high incidence of hemorrhage observed in some studies using antivascular agents has precluded the further development of these drugs for recurrent or metastatic nasopharyngeal carcinoma (NPC).
- Major late complication rates as high as 35% have been reported in some retreatment series, stressing the need to restrict these approaches to a very select patient population treated in centers with expertise.

Qualifying Statements

Qualifying Statements

- The American College of Radiology (ACR) Committee on Appropriateness Criteria (AC) and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
- ACR seeks and encourages collaboration with other organizations on the development of the ACR AC through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Saba NF, Salama JK, Beitler JJ, Busse PM, Cooper JS, Jones CU, Koyfman S, Quon H, Ridge JA, Siddiqui F, Worden F, Yao M, Yom SS, Expert Panel on Radiation Oncologyâ€“Head & Neck Cancer. ACR Appropriateness CriteriaÂ® nasopharyngeal carcinoma. Reston (VA): American College of Radiology (ACR); 2015. 13 p. [69 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Head & Neck Cancer

Composition of Group That Authored the Guideline

Panel Members: Nabil F. Saba, MD (*Principal Author*); Joseph K. Salama, MD (*Panel Vice-chair*); Jonathan J. Beitler, MD, MBA; Paul M. Busse, MD, PhD; Jay S. Cooper, MD; Christopher U. Jones, MD; Shlomo Koyfman, MD; Harry Quon, MD, MS; John A. Ridge, MD, PhD; Farzan Siddiqui, MD, PhD; Francis Worden, MD; Min Yao, MD, PhD; Sue S. Yom, MD, PhD (*Panel Chair*)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American College of Radiology (ACR) Web site .

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Oct. 3 p. Available from the American College of Radiology (ACR) Web site .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Evidence table development. Reston (VA): American College of Radiology; 2015 Nov. 5 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Topic development process. Reston (VA): American College of Radiology; 2015 Nov. 2 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Rating round information. Reston (VA): American College of Radiology; 2015 Apr. 5 p. Available from the ACR Web site .

- ACR Appropriateness Criteria® nasopharyngeal carcinoma. Evidence table. Reston (VA): American College of Radiology; 2015. 37 p. Available from the ACR Web site .
- ACR Appropriateness Criteria® nasopharyngeal carcinoma. Literature search. Reston (VA): American College of Radiology; 2015. 2 p. Available from the ACR Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 12, 2016.

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